(P1/1), 93 to 103 (P5), 110 to 123 (P5/1), 138 [142] to 166 (P2) and 152 to 166 (P2/1) in accordance with the numbering of the amino-acid positions of natural EPO, comprising:

a) immunizing an animal with said peptide; and

b) isolating said epitope-specific EPO antibodies.

9. (Amended) An anti-idiotype antibody against the binding region of an EPO-neutralizing antibody as claimed in claim 6 [8].

14. (Twice Amended) A pharmaceutical composition containing an epitope-specific anti-EPO antibody as claimed in claim 6 [8] and a pharmaceutically acceptable excipient.

17. (Amended) An anti-erythropoietin (EPO) antibody directed against epitopes that bind [binds] to the EPO receptor.

23. (Amended) An anti-EPO antibody as claimed in claim 6 [5], which is directed against epitopes which bind to the EPO receptor.

REMARKS

Claims 5-7, 9-12, and 14-23 are pending. Claim 5 has been amended to clarify the start point of the claimed P2 peptide. Support for this amendment may be found on page 3 of the amended specification. Claims 9 and 14 have been amended to clearly define the claimed invention, as they no longer depend on canceled claim 8 and now depend on independent claim 6. Support for this amendment may be found on pages 7 and 17-18 of the specification. Claim 17 has been amended to properly describe the claimed invention. Claim 23 has been amended to depend on claim 6, which recites an anti-EPO antibody. These amendments do not constitute

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

issues of new matter. Applicants address each outstanding rejection under its respective statutory section below.

Rejection Under 35 U.S.C. § 101

Applicants gratefully acknowledge the Office's withdrawal of its rejection of claim 10, as being drawn to non-statutory subject matter, in light of the previously submitted amendment.

Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 9 and 14-16 stand rejected as containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to make or use the invention. Specifically, the Office notes that these claims are defined by claim 8, which has been canceled. Accordingly, Applicants have amended claims 9 and 14 to depend on independent claim 6. Applicants assert that this amendment now distinctly describes the claimed invention and respectfully request reconsideration and withdrawal of this rejection.

Rejection Under 35 U.S.C. § 112, Second Paragraph

Applicants gratefully acknowledge the Office's withdrawal of its previous rejection of claims 5, 17, and 23 in light of the previously submitted amendment.

Claim 5 stands rejected as vague and indefinite because this claim recites "142 to 166 (P2)" which is inconsistent with the definition of peptide P2 as described on page 3 of the amended specification. Applicants have amended claim 5 to recite "138 to 166 (P2)" which is now consistent with the amended specification. Reconsideration and withdrawal of this rejection is therefore respectfully requested.

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

Rejection Under 35 U.S.C. § 102(b)

Applicants gratefully acknowledge the Office's withdrawal of its rejection of claims 5, 6, 10-12, 18, and 23, as being anticipated by Lin et al. (U.S. Pat. No. 4,703,008) ("Lin"), in light of the previously submitted amendment.

Claims 17, 20, and 22 remain rejected as allegedly anticipated by Lin. The Office notes that these claims are drawn to antibodies that are not limited to any specific peptide and need not neutralize the biological activity of EPO. Based on this assertion, the Office maintains that antibodies generated to the peptides disclosed by Lin (col. 36) will "more likely than not" bind to a region of EPO that interacts with the EPO receptor.

Applicants respectfully traverse this rejection. In proposing this argument, the Office invokes the principle of inherency that the antibodies of Lin would inherently contain the antibodies of claim 17. As described by the Federal Circuit, "[i]nherency . . . may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *See In re Oelrich*, 666 F.2d 578, 581, 212 U.S.P.Q. 323, 326 (C.C.P.A. 1981) (quoting *Hansgirg v. Kemmer*, 26 C.C.P.A. 937, 102 F.2d 212, 214, 40 U.S.P.Q. (BNA) 665, 667 (C.C.P.A 1939)). Furthermore, to invoke the principle of inherency, an Examiner "must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic *necessarily* flows from the teachings of the applied prior art." *See Ex parte Levy*, 17 U.S.P.Q. 2d 1461, 1464 (Bd. Pat. App. & Int. 1990) (emphasis added). The Office's use of the phrase "more likely than not" implies that the possible presence of the claimed antibodies in Lin's antibody preparations is not necessarily a certainty,

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

but a mere possibility. The instant specification also supports this argument by stating that little is known about the mechanism of the interaction of EPO with its receptor, making it difficult to predict whether an antibody will target this domain (page 2, lines 20-21). As such, the Office's position fails to satisfy the strict requirements of inherency.

Moreover, the Office's observation that Lin's antibodies immunoprecipitate intact EPO does not necessarily demonstrate binding specifically to the domain of EPO that interacts with the EPO receptor. Lin provides no direct evidence that the antibodies generated to the disclosed peptides (col. 36) bind this EPO domain. Furthermore, Lin states that "[p]reliminary in vivo activity studies on the three peptides revealed no significant activity either alone or in combination" (col. 36, lines 34-36) which further undermines the Office's assertion that the antibodies generated by Lin bind to a region of EPO that interacts with the EPO receptor. Applicants therefore respectfully request reconsideration and withdrawal of this rejection in light of the above statements.

Claims 17, 18, 20, and 22 are rejected as allegedly anticipated by Sytkowski et al. (J.B.C. 262:1161, 1987) ("Sytkowski"). According to the Office, Sytkowski discloses antibodies against specific EPO peptides that bind to EPO and neutralize EPO activity. As with Lin, the Office uses these observations to conclude that, "more likely than not", these antibodies bind to regions of EPO that bind to the EPO receptor. Applicants respectfully traverse the Office's position for the following reasons.

First, Applicants assert that Sytkowski's antibodies do not inherently contain the antibodies of claims 17, 18, 20, and 22. Inhibition of EPO function does not necessarily imply

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

that these antibodies bind the EPO domain that binds the EPO receptor. Sytkowski discusses two other possible alternative explanations for how these antibodies may work (page 1165, last paragraph). In one instance, these antibodies may inhibit EPO activity not by binding the receptor epitopes on EPO, but by binding near them and sterically inhibiting or physically blocking the interaction of EPO with its receptor. In another instance, these antibodies may bind nowhere near the receptor domain on EPO, but many nonetheless inhibit EPO function by causing an allosteric change in the hormone molecule. Sytkowski presents no data that would distinguish between these possibilities.

Second, Sytkowski reported that the six peptides used to generate their antibodies failed to demonstrate any EPO biological activity and that these peptides failed to inhibit the biological activity of whole EPO. More importantly, these authors directly state that "none of these peptides react[s] directly with the erythropoietin receptor" (p.1162, right column, first full paragraph). These results clearly distinguish the antibodies disclosed in this referenced from the claimed antibodies that specifically call for epitopes that bind to the EPO receptor.

Third, the Office points to the use of immunoprecipitation by Sytkowski as grounds for alleged anticipation of claim 22, stating that Sytkowski discloses a method of purifying EPO using this method and the disclosed antibodies. For the above-mentioned reasons, the antibodies disclosed in Sytkowski are not inherently those claimed in claim 17 and thus used in dependent claim 22. Furthermore, Sytkowski employed this technique to determine if their antibodies bound EPO, not to purify the EPO glycoprotein as described in claim 22. For these reasons, Applicants respectfully request reconsideration and withdrawal of this rejection.

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, D. C. 20005
202-408-4000

Rejection Under 35 U.S.C. § 103(a)

Applicants gratefully acknowledge the Office's withdrawal of its rejection of claims 9, 14-16, as unpatentable over Lin, in light of the previously submitted amendment.

Claim 21 remains rejected as allegedly unpatentable over Lin. In maintaining this rejection over Applicants' previous arguments, set forth in the amendment of July 31, 1998, the Office refers to its argument that Lin's antibodies are inherently the same as the claimed antibodies. For the reasons stated above, Applicants respectfully assert that this argument does not satisfy the requirements needed to invoke the inherency principle. Applicants therefore respectfully request reconsideration and withdrawal of this rejection.

Claims 19 and 21 are rejected as allegedly unpatentable over Sytkowski. Specifically, the Office asserts that Sytkowski teaches antibodies that bind to EPO and neutralize EPO activity and that production of pharmaceutical antibodies and monoclonal antibodies, once Sytkowski's antibodies are generated would be well-known to one of ordinary skill in the art. For the above-stated reasons, Sytkowski does not disclose antibodies that specifically bind the EPO domain that recognizes the EPO receptor. Thus, Sytkowski's disclosure does not make obvious either the production of monoclonal antibodies specific for the EPO domain that recognizes the EPO receptor or corresponding pharmaceutical antibodies. Applicants therefore respectfully request reconsideration and withdrawal of this rejection.

Obviousness-Type Double Patenting

Claims 7 and 19 stand rejected for obviousness-type double patenting over claims 1 and 2 of U.S. Patent No. 5,712,370. Claims 6, 11, 17, 18, 20, and 21 are also rejected for obviousness-

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, D. C. 20005
202-408-4000

type double patenting as unpatentable over claims 1 and 2 of U.S. Patent No. 5,712,370. Applicants request that these rejections be held in abeyance until allowable subject matter has been indicated.

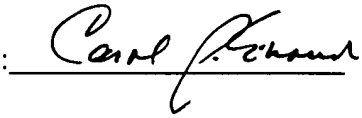
Applicants respectfully request that this Amendment be entered by the Office, placing claims 5-7, 9-12, and 14-23 in condition for allowance.

In view of the foregoing remarks, Applicants submit that their claimed invention, as amended, is not rendered obvious in view of the prior art references cited against this application. Applicants therefore respectfully request the entry of this Amendment, the Examiner's reconsideration and reexamination of the application, and the timely allowance of the pending claims.

Please grant any additional extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

By: 

Carol P. Einaudi
Reg. No. 32,220

Date: August 16, 2000

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, D.C. 20005
202-408-4000